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Research Article

**FORMULATION AND CHARACTERIZATION OF BILAYERED
BUCCAL TABLETS OF DIACEREIN****Manasa Chikkulla,^{1*} Dr. Rama Krishna Mungi¹, Dr. K. Balaji¹**¹Department of Pharmaceutics, Avanthi Institute of pharmaceutical Sciences, Hayathnagar,
R.R. Dist., Hyderabad**Abstract:**

Buccoadhesive Bilayer buccal tablets of Diacerein were prepared by using Cashew nut tree gum, Xanthan gum and Karayagum as mucoadhesive polymers. Nine formulations were developed with varying concentrations of polymers F1 to F9 formulations were composed of Cashew nut tree gum, Xanthan gum and Karayagum in ratios of 1:1, 1:2 and 1:3. The formulated mucoadhesive buccal tablets were assessed for quality attributes like weight variation, hardness, thickness, friability, drug content, moisture absorption, surface pH and in vitro drug release studies. Optimized formulation F4 showed maximum release of the drug (99.59%). The FTIR results showed no evidence of interaction between the drug and polymers. All the evaluation parameters given the positive result and comply with the standards. The results indicated that the mucoadhesive buccal tablets of Diacerein may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in bioavailability of Diacerein through buccal mucosa.

Key words: Diacerein, Cashew nut tree gum, Xanthan gum and Karayagum and Buccal tablets.

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INTRODUCTION:

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing. Problems such as first pass metabolism and drug degradation in the GIT environment can be circumvented by administering the drug via buccal route. Moreover, the oral cavity is easily accessible for self medication and be promptly terminated in case of toxicity by removing the dosage form from buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally via this route. Successful buccal drug delivery using buccal adhesive system requires at least three of the following (a) A bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa (b) A vehicle the release the drug at an appropriate rate under the conditions prevailing in the mouth and (c) Strategies for overcoming the low permeability of the oral mucosa. Buccal adhesive drug delivery stem promote the residence time and act as controlled release dosage forms.

The use of many hydrophilic macromolecular drugs as potential therapeutic agents is their in adequate and erratic oral absorption. However, therapeutic potential of these compounds lies in our ability to design and achieve effective and stable delivery systems. Based on our current understanding, it can be said that many drugs can not be delivered effectively through the conventional oral route.

The main reasons for the poor bio-availability of many drugs through conventional oral route are:

- ✓ Pre-systemic clearance of drugs.
- ✓ The sensitivity of drugs to the gastric acidic environment which leads to gastric irritation. Limitations associated with gastro intestinal tract like variable absorption characteristics.

Buccal mucosa composed of several layers of different cells. The Epithelium is similar to stratified squamous epithelia found in rest of the at least one of which is biological nature are held together by means of interfacial forces.¹

Buccal drug delivery is a type of bioadhesive drug delivery especially it is a mucoadhesive drug delivery system is adhered to buccal mucosa.

- The term bioadhesion is commonly defined as an adhesion between two materials where at least one of the materials is of biological origin. In the case of bioadhesive drug delivery systems, bioadhesion often refers to the adhesion between the excipients of the formulation (i.e. the inactive media) and the biological tissue.

- The term mucoadhesion can be considered to refer to a sub group of bioadhesion and, more specifically, to the case when the formulation interacts with the mucous layer that covers a mucosal tissue.

The mucosal layer lines a number of regions of the body including gastrointestinal tract, urogenital tract, airway, ear, nose and eye. Hence mucoadhesive drug delivery system includes the following:

1. Buccal delivery system
2. Oral delivery system
3. Ocular delivery system
4. Vaginal delivery system
5. Rectal delivery system
6. Nasal delivery system²

Overview of the Oral Mucosa Structure The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer^{18, 19} can be seen in figure 1. The epithelium of the buccal mucosa is about 40- 50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The turnover time for the buccal epithelium has been estimated at 5-6 days³, and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm , while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 μm . The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized⁴. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, nonkeratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and only have small amounts of ceramide⁵⁻⁷. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

Permeability

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the

permeability of the buccal mucosa is 4-4000 times greater than that of the skin⁸. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

Environment

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principle components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association or some maybe attached to certain regions on the cell surfaces. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another⁹. Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems.

Ideal Characteristics of Buccal Drug Delivery System¹⁰

- ✓ Should adhere to the site of attachment for a few hours.
- ✓ Should release the drug in a controlled fashion.
- ✓ Should provide drug release in a unidirectional way toward the mucosa.
- ✓ Should facilitate the rate and extent of drug absorption.
- ✓ Should not cause any irritation or inconvenience to the patient.
- ✓ Should not interfere with the normal functions such as talking and drinking.

MECHANISM OF MUCOADHASIVE:

Several theories have been put forward to explain the mechanism of polymer–mucus interactions that lead to mucoadhesion. To start with, the sequential events that occur during bioadhesion include an intimate contact between the bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive. Following this is the penetration of the bioadhesive into the tissue crevices, interpenetration between the mucoadhesive polymer chains and those of the mucus. Subsequently low chemical bonds can

become operative. Hydration of the polymer plays a very important role in bioadhesion. There is a critical degree of hydration required for optimum bioadhesion. If there is incomplete hydration, the active adhesion sites are not completely liberated and available for interaction. On the other hand, an excessive amount of water weakens the adhesive bond as a result of an overextension of the hydrogen bonds. During hydration; there is a dissociation of hydrogen bonds of the polymer chains. The polymer–water interaction becomes greater than the polymer–polymer interaction, thereby making the polymer chains available for mucus penetration. Following polymer hydration intermingling between chain segments of the mucoadhesive polymer with the mucus occurs. The factors critical for this model of mucoadhesion are the diffusion coefficient of the polymer, contact time and contact pressure. The polymer diffusion coefficient is influenced by the molecular mass between cross-links, and is inversely related to the cross-linking density.¹¹⁻¹⁴

MATERIALS

Diacerein (Procured From Lark laboratories, Bhiwadi, India.) Provided by SURA LABS, Dilsukhnagar, Hyderabad. Cashew nut tree gum from Zydus Cadila, Ahmedabad ,Xanthan gum from Acurate Pharma, Karayagum from Sd fine Chem.Ltd. Mumbai,MCC from Chemdie Corporation, Magnesium stearate from Chemdie Corporation, Talc from Sd fine Chem.Ltd. Mumbai, Saccharin sodium from Sd fine Chem.Ltd. Mumbai

METHODOLOGY

Analytical method used in the determination of Diacerein

Preparation of 0.2M Potassium Dihydrogen Orthophosphate Solution:

Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution:

Accurately weighed 8 gm of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed

Preparation of pH 6.8 phosphate buffer:

Accurately measured 250 mL of 0.2M potassium dihydrogen ortho phosphate and 112.5 mL of 0.2M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Preparation of pH 7.4 phosphate buffer:

Accurately measured 250 mL of 0.2M potassium

dihydrogen ortho phosphate and 195.5 mL of 0.2M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Preparation of standard graph in phosphate buffer pH 6.8

100 mg of Pure drug was dissolved in small amount of Methanol (5-10 ml), allowed to shake for few minutes and then the volume was made up to 100ml with phosphate buffer pH 6.8, from this primary stock (1mg/ml), 10 ml solution was transferred to another volumetric flask made up to 100 ml with phosphate buffer pH 6.8. From this secondary stock 0.2, 0.4, 0.6, 0.8, 1, ml was taken separately and made up to 10 ml with phosphate buffer pH 6.8 to produce 2, 4, 6, 8, 10 µg/ml respectively. The absorbance was measured at 252 nm using a UV spectrophotometer. Standard calibration curve values The standard calibration curve of Diacerein in phosphate buffer pH 6.8

Preparation of standard graph in phosphate buffer pH 7.4

100 mg of drug was dissolved in small amount of phosphate buffer and make the volume up to 100ml with phosphate buffer pH 7.4, from this primary stock(1mg/ml), 10 ml solution was transferred to another volumetric flask made up to 100 ml with phosphate buffer pH 7.4. From this secondary stock 0.2, 0.4, 0.6, 0.8, 1 ml were taken separately and made up to 10 ml with phosphate buffer pH 7.4, to produce 2, 4, 6, 8, 10 µg/ml respectively. The absorbance was measured at 252 nm using a UV spectrophotometer. The standard calibration curve of Diacerein in phosphate buffer pH 7.4 .

Solubility Studies

The solubility of Diacerein in phosphate buffer solution pH 6.8 was determined by phase equilibrium method. An excess amount of drug was taken into 20

ml vials containing 10 ml of phosphate buffers (pH 6.8). Vials were closed with rubber caps and constantly agitated at room temperature for 24 hr using rotary shaker. After 24 hr, the solution was filtered through 0.2µm Whatman's filter paper. The amount of drug solubilized was then estimated by measuring the absorbance at 252 nm using a UV spectrophotometer.

The standard curves for Diacerein were established in phosphate buffers (pH 6.8) and from the slope of the straight line the solubility of Diacerein was calculated. The studies were repeated in triplicate (n = 3), and mean was calculated.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel.

Table 1: Formulation composition for tablets

INGREDIENTS (MG)	FORMULATION CODES								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diacerein	50	50	50	50	50	50	50	50	50
Cashew nut tree gum	25	50	75	-	-	-	-	-	-
Xanthan gum	-	-	-	25	50	75	-	-	-
Karaya gum	-	-	-	-	-	-	25	50	75
Ethyle cellulose (Backing Layer)	40	40	40	40	40	40	40	40	40
MCC	61	36	11	61	36	11	61	36	11
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	5	5	5	5	5	5	5	5	5
Saccharin sodium	15	15	15	15	15	15	15	15	15
Total weight	200	200	200	200	200	200	200	200	200

All the quantities were in mg

RESULTS AND DISCUSSION:**Solubility Studies:****Table 2: Solubility studies**

S.No	Medium	Amount present ($\mu\text{g/mL}$)
1	Phosphate pH 6.8 buffer	98.12
2	Phosphate pH 7.4 buffer	96.53

Standard graph in phosphate buffer pH 6.8 (λ_{max} 252 nm)

Standard graph of Diacerein was plotted as per the procedure in experimental method and its linearity is shown in Table 9.2 and Fig 9.1. The standard graph of Diacerein showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

Table 3: Standard graph values of Diacerein in pH 6.8 phosphate buffer

Concentration ($\mu\text{g/mL}$)	Absorbance
0	0
2	0.143
4	0.259
6	0.378
8	0.511
10	0.629

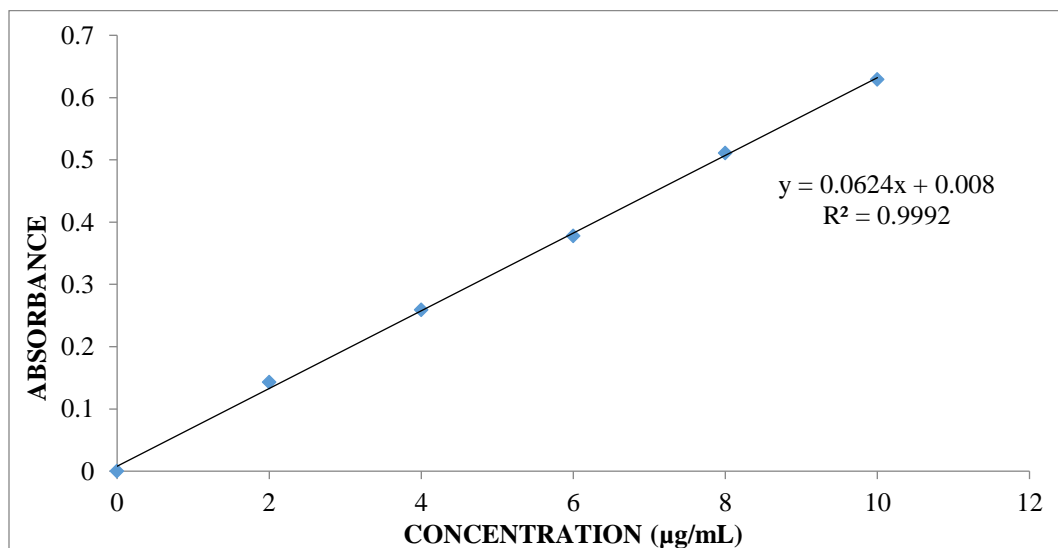
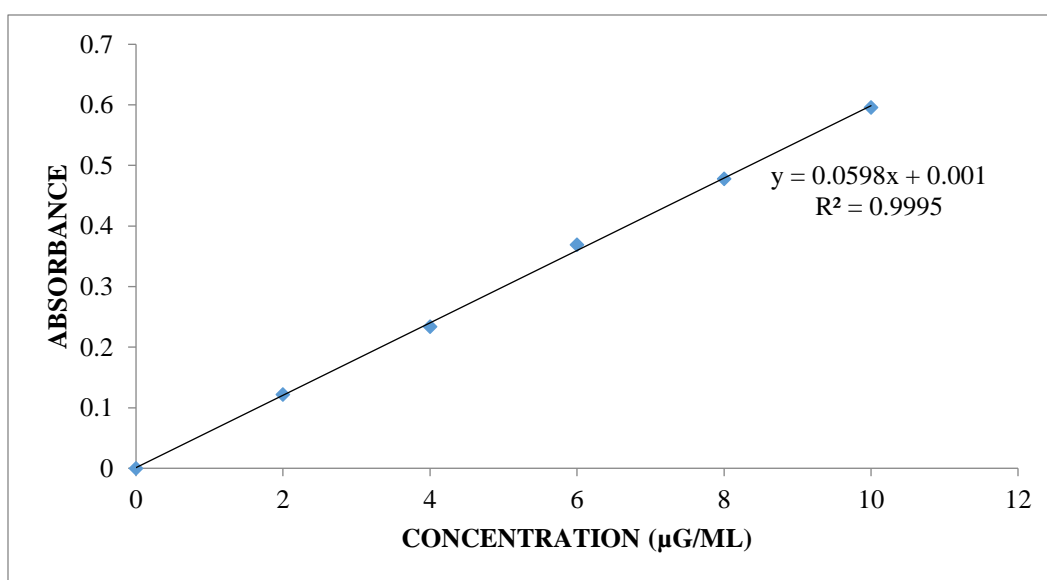
**Fig 1: Standard graph of Diacerein in pH 6.8 phosphate buffer**

Table 4: Standard graph values of Diacerein in pH 7.4 phosphate buffer

Concentration ($\mu\text{g/mL}$)	Absorbance
0	0
2	0.122
4	0.234
6	0.369
8	0.478
10	0.596

**Fig 2: Standard graph of Diacerein in pH 7.4 phosphate buffer**
Preformulation parameters of powder blend**Table5: Pre-formulation parameters of blend**

Formulation Code	Angle of repose (Θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
F1	28.75	0.481	0.572	15.90	1.18
F2	27.33	0.475	0.566	16.07	1.19
F3	25.38	0.524	0.599	12.52	1.14
F4	26.43	0.412	0.483	14.69	1.17
F5	24.77	0.488	0.537	9.12	1.10
F6	26.42	0.439	0.521	15.73	1.18
F7	28.19	0.559	0.649	13.94	1.16
F8	29.58	0.331	0.393	15.77	1.18
F9	28.73	0.362	0.428	15.42	1.18

All the values represent n=3

Quality control parameters for tablets:

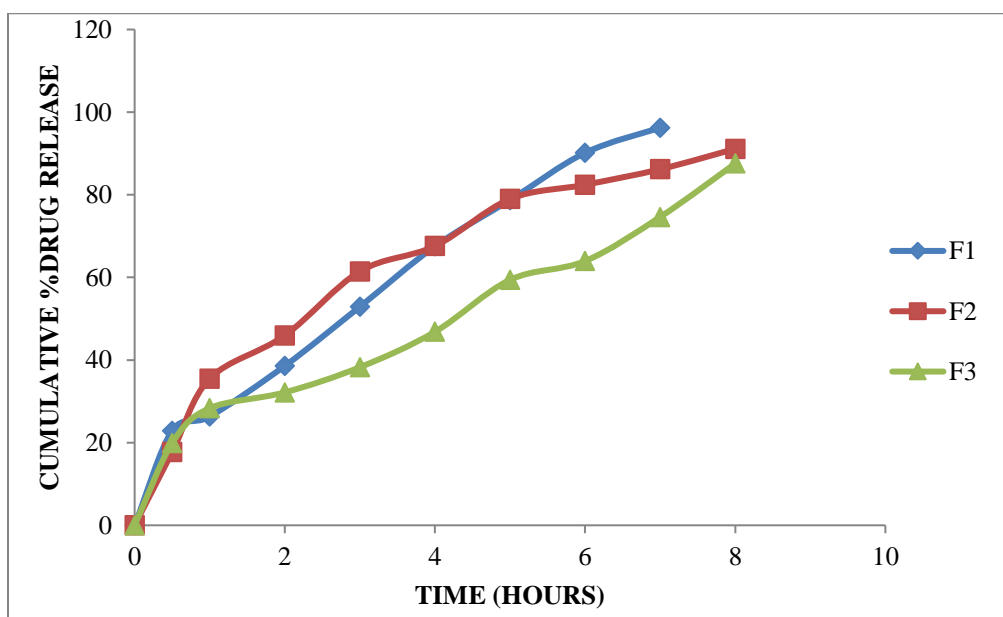
Table6: *In vitro* quality control parameters

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm ²)	Friability (%)	Content uniformity (%)
F1	198.47	4.01	4.9	0.56	96.10
F2	196.92	4.92	4.0	0.36	98.65
F3	199.30	4.35	5.3	0.24	99.10
F4	197.12	4.87	4.1	0.68	97.34
F5	198.82	4.28	5.2	0.59	98.58
F6	199.27	4.13	5.6	0.32	96.14
F7	200.04	4.79	4.1	0.77	99.82
F8	198.75	4.35	5.0	0.62	95.38
F9	197.80	4.60	4.8	0.43	98.76

In Vitro Drug Release Studies

Table7: Dissolution data of Floating tablets

TIME (H)	CUMULATIVE PERCENTE OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	22.89	17.72	19.90	26.12	14.82	13.92	15.05	13.53	11.58
1	26.32	35.50	28.35	32.83	24.73	20.03	23.19	18.92	20.16
2	38.58	45.93	32.17	41.51	35.90	27.51	30.27	28.60	26.09
3	52.91	61.46	38.26	49.15	47.17	35.99	36.59	37.18	34.10
4	67.54	67.59	46.83	56.99	58.34	46.42	49.01	46.82	53.23
5	78.73	78.98	59.41	67.31	64.10	55.60	55.39	52.99	57.42
6	90.15	82.42	63.96	74.65	70.09	63.17	75.53	67.76	65.99
7	96.21	86.18	74.63	82.09	75.37	70.96	85.89	77.14	76.37
8		91.13	87.57	99.59	87.24	75.12	93.73	87.34	81.83

Fig 3: *In vitro* dissolution data for formulations F1 – F3 by using Cashew nut tree gum polymer

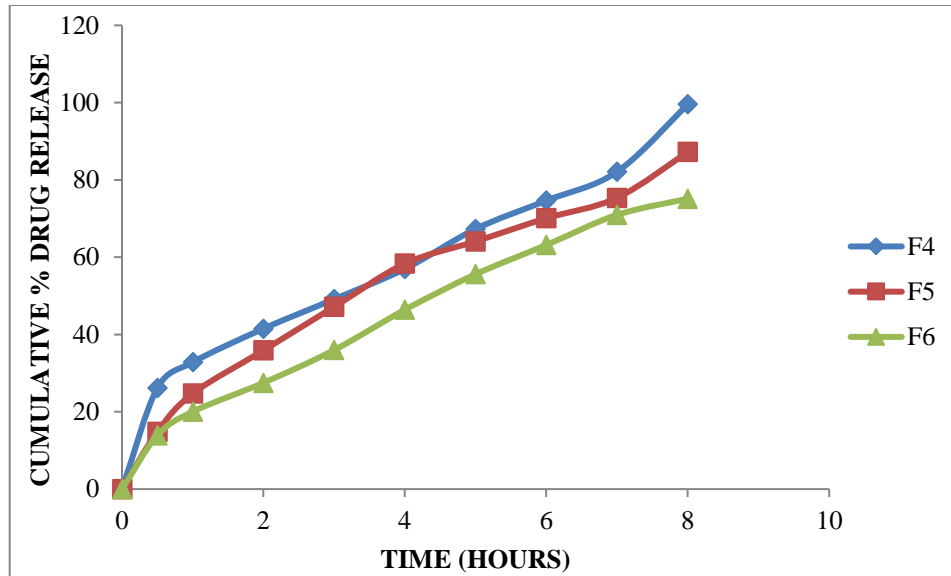


Fig 4: In vitro dissolution data for formulations F4 –F6 by using Xanthan gum polymer

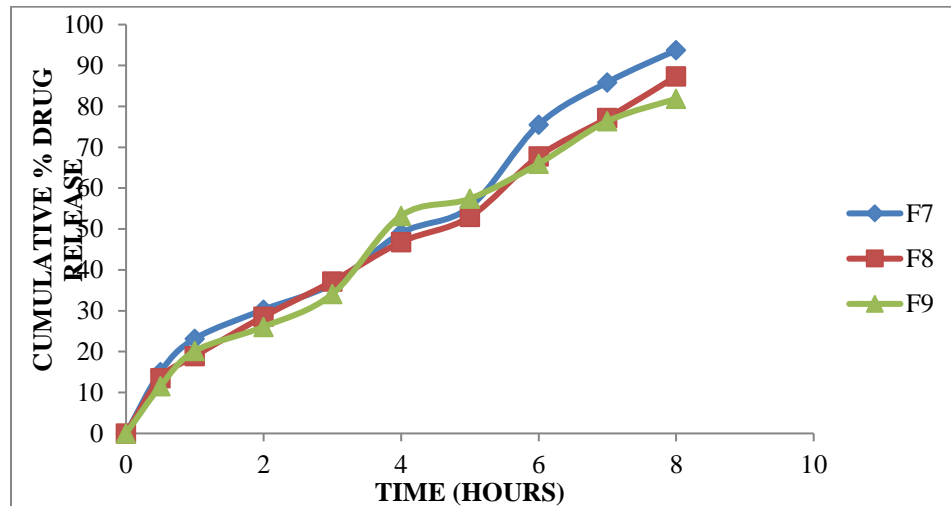


Fig 5: In vitro dissolution data for formulations F7- F9 by using Karaya gum polymer

Table 8: Release Kinetics:

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
26.12	0.5	0.707	1.417	0.301	1.869	52.240	0.0383	-0.583	73.88	4.642	4.196	0.446
32.83	1	1.000	1.516	0.000	1.827	32.830	0.0305	-0.484	67.17	4.642	4.065	0.577
41.51	2	1.414	1.618	0.301	1.767	20.755	0.0241	-0.382	58.49	4.642	3.882	0.760
49.15	3	1.732	1.692	0.477	1.706	16.383	0.0203	-0.308	50.85	4.642	3.705	0.937
56.99	4	2.000	1.756	0.602	1.634	14.248	0.0175	-0.244	43.01	4.642	3.504	1.138
67.31	5	2.236	1.828	0.699	1.514	13.462	0.0149	-0.172	32.69	4.642	3.197	1.444
74.65	6	2.449	1.873	0.778	1.404	12.442	0.0134	-0.127	25.35	4.642	2.938	1.704
82.09	7	2.646	1.914	0.845	1.253	11.727	0.0122	-0.086	17.91	4.642	2.616	2.025
99.59	8	2.828	1.998	0.903	-0.387	12.449	0.0100	-0.002	0.41	4.642	0.743	3.899

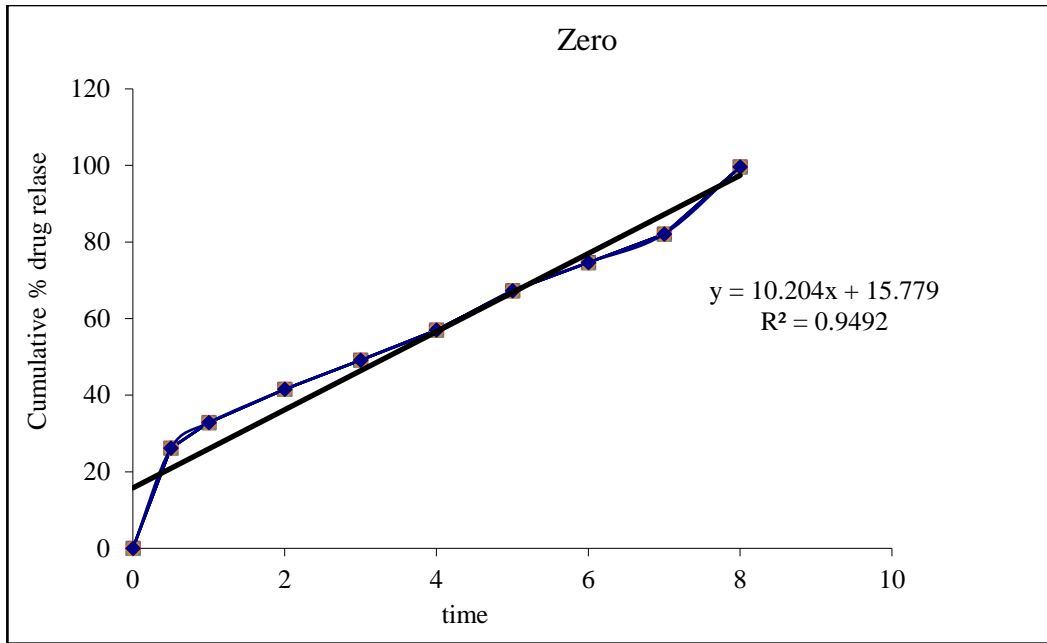


Fig 9.6: Zero order plot of optimized formulation

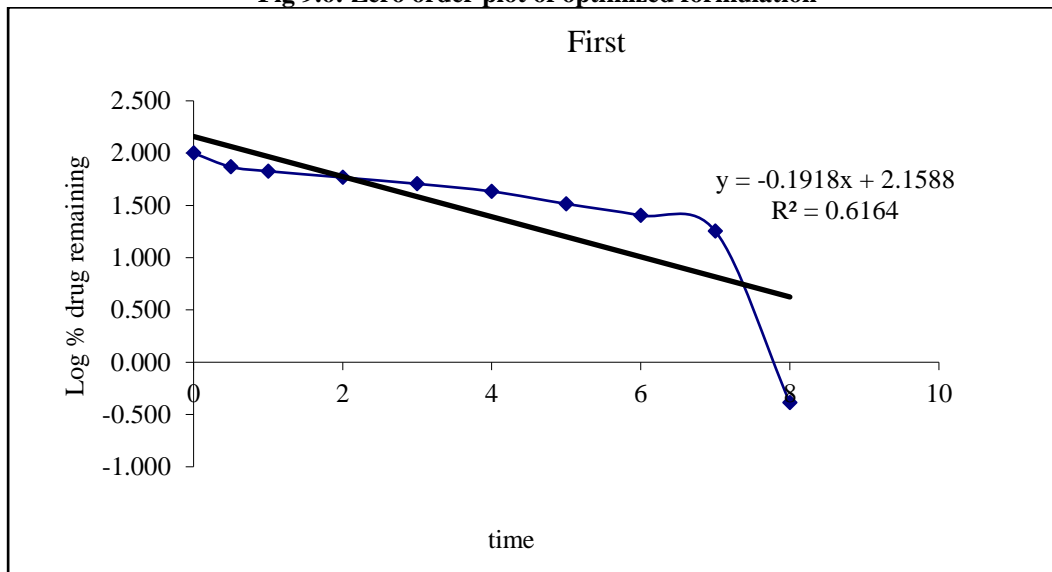


Fig 9.7: First order plot of optimized formulation

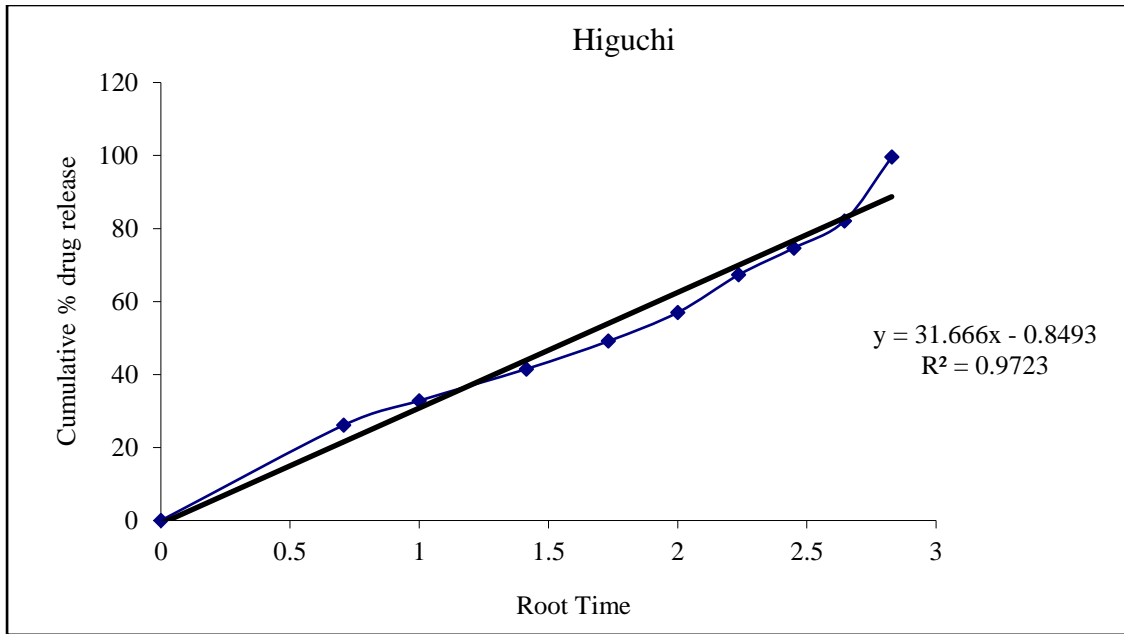


Fig 9.8: Higuchi plot of optimized formulation

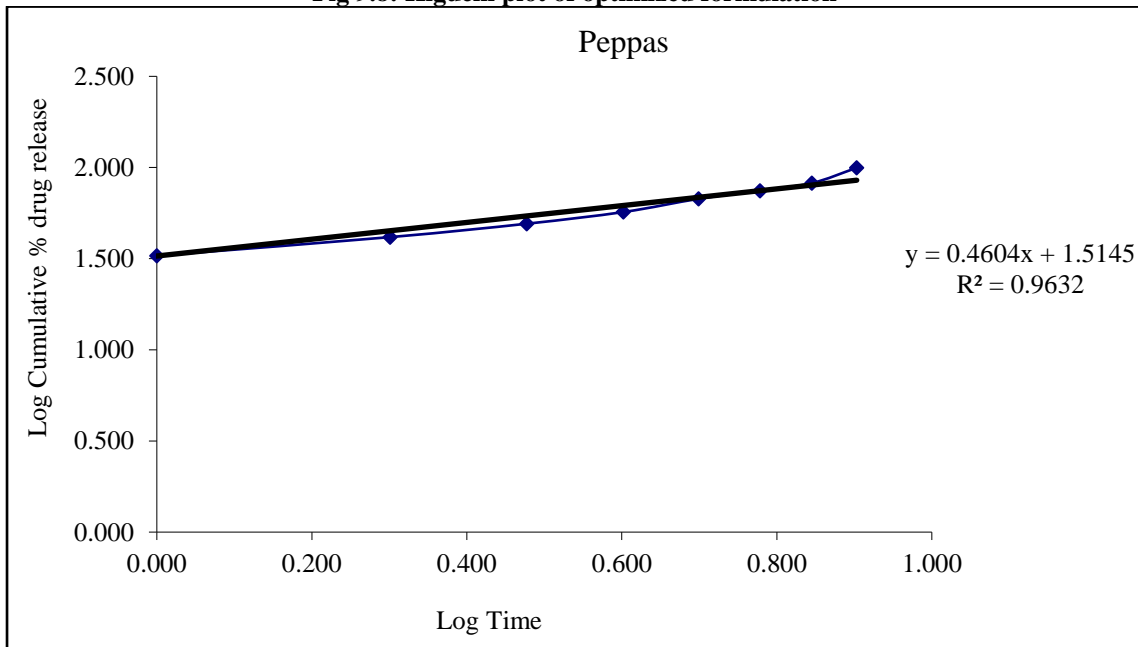


Fig 9.9: Koresmeyer-peppas plot of optimized formulation.

Drug – Excipient compatibility studies
Fourier Transform-Infrared Spectroscopy:

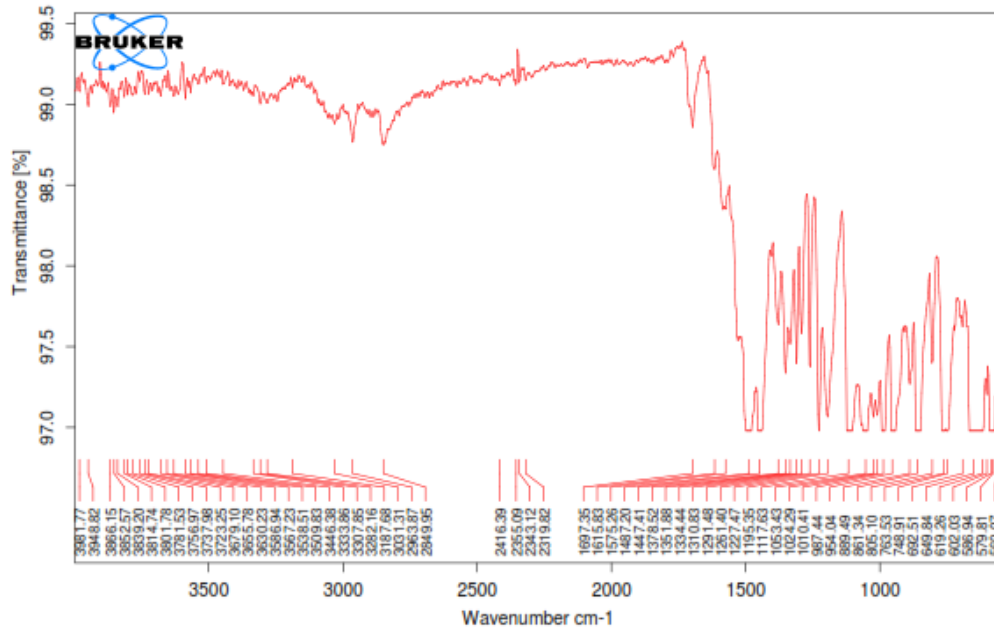


Fig 9.10: FTIR Peak of pure drug Diacerein

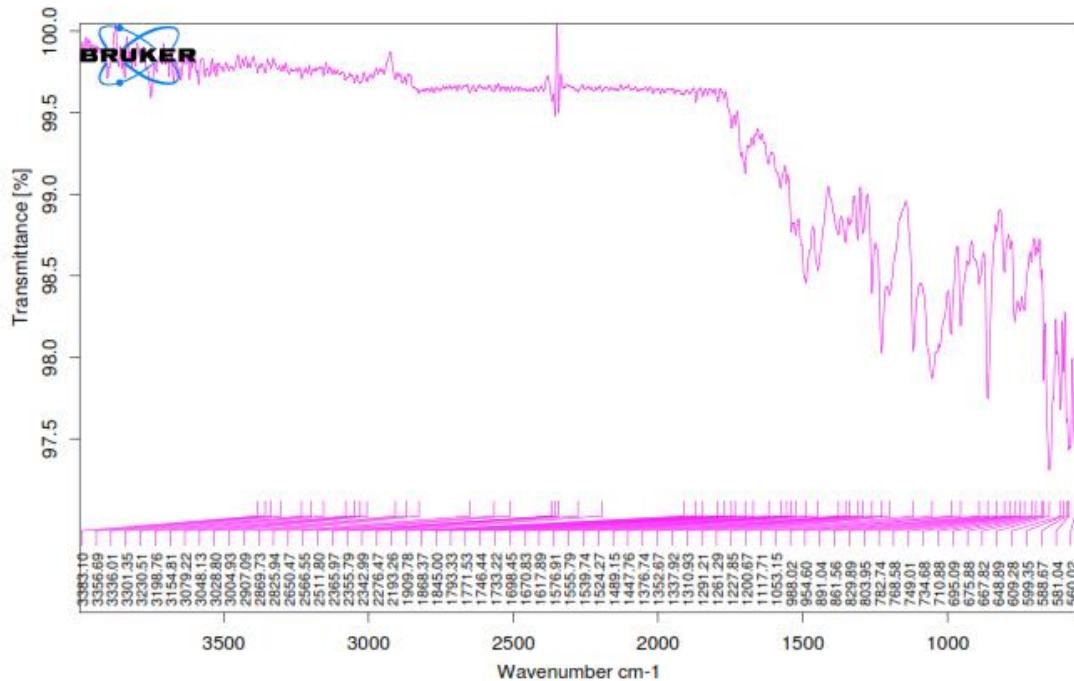


Fig 9.11: FTIR Peak of Optimised formulation

CONCLUSION:

The present research was carried out to develop mucoadhesive bilayer buccal tablets of Diacerein using various polymers. The preparation process was simple, reliable and inexpensive. All the prepared tablet formulations were found to be good without

capping and chipping. The mucoadhesive buccal tablets of Diacerein could be prepared using Cashew nut tree gum, Xanthan gum and Karaya gum polymers by using direct compression method. The prepared mucoadhesive buccal tablets subjected to infrared spectrum study suggested that there was no

drug -polymer interaction. All the prepared tablets were in acceptable range of weight variation, hardness, thickness, friability and drug content as per pharmacopeial specification. The surface pH of prepared buccal tablets was in the range of salivary pH, suggested that prepared tablets could be used without risk of mucosal irritation. The *in-vitro* release of Diacerein was extended for 8 h. Formulations F4 batch shows good *in vitro* drug release 99.59%. From the results of present investigation it can be concluded that Diacerein can certainly be administered through the oral mucosa and Xanthan gum is suitable for development of buccoadhesive system.

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